BABEŞ-BOLYAI UNIVERSITY
CLUJ-NAPOCA

Faculty of Chemistry
and Chemical Engineering

Ph.D. Thesis Abstract

Béla MIHÁLY

METAL COMPLEXES OF 9-METHYLADENINE AND THEOPHYLLINE

Scientific Advisors:

Prof. Dr. Ionel Haiduc

Prof. Dr. Ioan Silaghi-Dumitrescu†

Cluj-Napoca

2013

Scientific committee:

Scientific advisors: Prof. Dr. Ionel Haiduc, Babes-Bolyai University, Cluj-Napoca
Prof. Dr. Ioan Silaghi-Dumitrescu, Babes-Bolyai University, Cluj-Napoca

President: Prof. Dr. Luminița Silaghi-Dumitrescu, Babes-Bolyai University, Cluj-Napoca
Reviewer: Prof. Dr. Bernhard Lippert, Technical University Dortmund, Dortmund
Reviewer: CSI Dr. Otilia Costișor, Institute of Chemistry Timisoara of Romanian Academy, Timisoara
Reviewer: Assoc. Prof. Dr. Edit Forizs, Babes-Bolyai University, Cluj-Napoca

Date of defence: **13 July, 2013**

Table of contents

Aims and outline of this thesis

This thesis deals with the joint uses of theoretical and experimental studies of some mixed ligand complexes of two model compounds, 9-methyladenine and theophylline.

The dissertation is structured in a first part consisting of a literature survey, followed by a presentation of the original results and a description of synthetic routes followed for the preparation of complexes and appendices.

Chapter 1 provides an introduction into the coordination chemistry of nucleobases and their derivatives, followed by a short description of the ligands, and presenting the wide variety of binding modes of 9-methyladenine and theophylline ligands to metal ions.

The following chapters are intended to present the original results on coordination chemistry of 9-methyladenine (**Chapter 2**) and theophylline (**Chapter 3**). In the present work we have used a variety of techniques in an attempt to elucidate their stereochemistries, being characterized by infrared and NMR spectroscopy, elemental analysis, Raman spectroscopy and by thermal methods (TG and DSC). In the near-infrared region of IR spectrum of theophylline complexes, we have assigned bands to the N−H and C=O stretching vibrational modes. We have used these bands to study the behavior of the ligands in their complexes.

In the case of 15 complexes, the geometry assigned is supported by X-ray diffraction, as well. Hydrogen bonding and outer sphere effects are important here. Solid state effects, hydrogen bonding, the outer coordination sphere, steric interactions and bonding are being described.

Keywords

Cadmium(II) complexes, copper(II) complexes DFT calculations, hydrothermal synthesis, 9-methyladenine, nucleobase, platinum(II) complexes, theophylline, zinc(II) complexes

Chapter I.

Metal-DNA interactions. Literature survey

This chapter is intended to describe the history, principles, recent developments and perspectives in the field of nucleobase coordination chemistry, which has grown exponentially during the last decades. The reasons for choosing nucleobases as models for study the interaction of metal ions with nucleic acids, at the molecular level, are the following: the products can be synthesized, isolated, purified and characterized more easily.

1. Introduction to the chemistry of nucleobases and their derivatives. General aspects

The five main natural nucleobases have fascinated the scientists over the last decades, owing to their role in the structure of nucleic acids, probably the world's most intriguing, most studied and most important molecules. This chapter will give an introduction to the chemistry of nucleobases, and their interactions with metal ions.

The nucleobases are derivatives of two possible ring structures, purine and pyrimidine, and are numbered according to their parent compound. They are the key components that confer variability to nucleic acids.

The most common bases are the two purine and three pyrimidine derivatives listed below: adenine (Ade, A), guanine (Gua, G) (purine bases), thymine (Thy, T), cytosine (Cyt, C) and uracil (Ura, U) (pyrimidine bases). During the last fourty years, more than 600 metal–nucleobase complexes have been prepared and crystallographically characterized. In recent years, the number of crystal structures for metal ions having nucleobases as ligands has increased dramatically. This can be explained by the structural characteristics of nucleobases: by allowing extension beyond basic coordination chemistry, larger and more complex molecular architectures based on the formation of supramolecules (formed exclusively through coordinate bond formation involving the nucleobases, or those self-assembled through complementary hydrogen bonding of nucleobases acting as ligands to metal centres) are possible [1]. Architectures based on these systems have a potential for applications due to their useful properties: acting as hosts for various molecule and ions, displaying optical properties, providing porous materials or having catalytic activity [1].

9-Methyladenine

9-Methyladenine contains three endocyclic nitrogen atoms, of which the two principal co-ordination sites are the *N1* and *N7* atoms. However, examples in which also other nitrogen atoms are involved in coordination, are known as well. There are several consequences of methylation of adenine at *N9* position:

- By substitution of the hydrogen atom bonded to *N9* atom of adenine, the coordination properties of other nitrogen donor sites can be explored in more details;
- Coordination of 9-alkyladenines at *N7* donor site (*e.g*. $\mathrm{Pt^{II}}$ binding), combined with a simultaneous coordination at *N1*, affects the acidity of the exocyclic amino group (about 10^9 fold increase of its acidity) [2, 3].

Theophylline

Theophylline is one of the biologically important N-methylated xanthines, which are of interest to researchers in quite diverse fields of study. It has often been substituted for guanine in model studies of metal-nucleotide interactions [4, 5]. Transition metal complexes of theophylline may serve as model compounds for the interaction between metal ions and oxopurine bases of nucleic acids. The most intensively studied portion of guanine with regard to metal–DNA interactions is the *N7*/*O6* region, considered to be the primary site of attachment of platinum antitumor drugs. Theophylline contains four potential binding sites (*N7*, *N9*, *C6*=O and *C2*=O), while the *N1* and *N3* sites are blocked by the methyl groups. According to previous studies, theophylline coordinates as a monodentate ligand in neutral media *via N9*, while in basic media *N7* can become the reactive site, as a result of the formation of $\mathrm{tp^-}$ theophyllinate anion [6, 7, 8, 9, 10], following removal of the weakly acidic *N7*–H proton ($\mathrm{p}K_\mathrm{a} = 8.5$) [11]. Theophylline, like the "basic" nucleobases, is ideally suited as building block for supramolecular coordination chemistry due to its versatility as ligand. This can be explained by three major properties: [1]

- The large number of donor sites available for metal binding,
- The hydrogen bonding donor/acceptor sites, and
- The potential for stacking (π–π or due to electrostatic forces), analogous to that observed in helical duplex DNA.

Chapter II.

Original contributions on coordination chemistry of 9-methyladenine

Aim of the Project

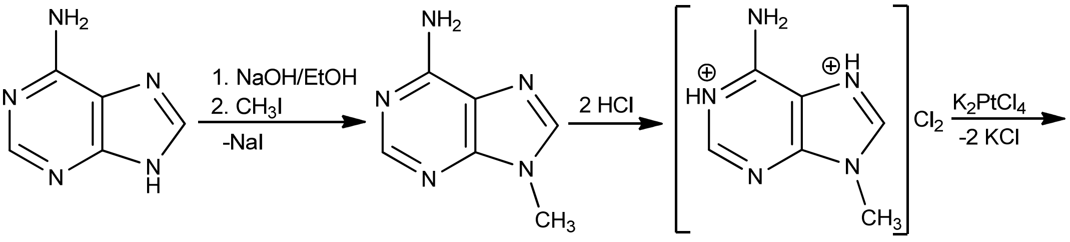
The goal of this work was the synthesis and characterization of a series of mixed-metal nucleobase complexes containing the *trans*-[(NH$_3$)$_2$Pt[(*N1*-9-MeA$^-$-*N7*)$_2${Pt(NH$_3$)$_3$}$_2$] unit. First, compounds 9-MeA (**1**) [12], [PtCl$_3$(9-MeAH-*N7*)] (**2**) [13], and [Pt(NH$_3$)$_3$(9-MeA-*N7*)]Cl$_2$ (**3**), [Pt(NH$_3$)$_3$(9-MeA-*N7*)](ClO$_4$)$_2$ (**4**), [Pt(NH$_3$)$_3$(9-MeA-*N7*)](NO$_3$)$_2$ (**5**) and *trans*-[Pt(NH$_3$)Cl$_2$] (**6**) [14] were prepared, according to the literature methods.

Therefore, *trans*-[(NH$_3$)$_2$Pt[(*N1*-9-MeA-*N7*)Pt(NH$_3$)$_3$]$_2$] (ClO$_4$)$_6$·2H$_2$O (**7**) was synthesized and characterized both in the solid state and in aqueous solution. The trinuclear *trans*-[(NH$_3$)$_2$Pt[(*N1*-9-MeA-*N7*)Pt(NH$_3$)$_3$]$_2$](ClO$_4$)$_6$·2H$_2$O (**7**) compound was reacted with Hg^{II}- and Cu^{II}-acetates, yielding complexes of type *trans*-[(NH$_3$)$_2$Pt[(*N1*-9-MeA$^-$-*N6,N7*)Pt(NH$_3$)$_3$]$_2${M(H$_2$O)$_2$}] (ClO$_4$)$_6$ (M = Hg (**8**), and Cu (**9**)) were obtained. For all complexes, the X-ray structures were established.

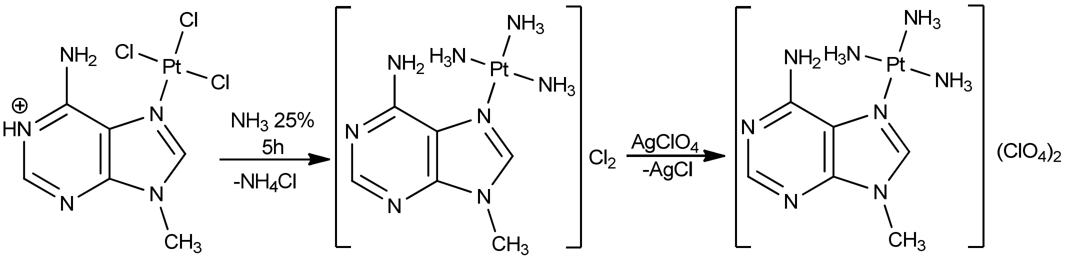
Results and Discussion

[Pt(NH$_3$)$_3$(9-MeA-*N7*)](ClO$_4$)$_2$ (7), and *trans*-[Pt(NH$_3$)$_2$(H$_2$O)$_2$](ClO$_4$)$_2$ (6’)

trans-[Pt(NH$_3$)$_2$(H$_2$O)$_2$](ClO$_4$)$_2$ (**6’**) was prepared *in situ* in water from *trans*-[Pt(NH$_3$)$_2$Cl$_2$] and 2 equivalents of Ag$^+$. Complexes of type [Pt(NH$_3$)$_3$(9-MeA-*N7*)]X$_2$ (X = ClO$_4$ (**4**) or NO$_3$ (**5**)) were prepared according to **Scheme 1**.



1



2 **3** **4**

Scheme 1

Eventually, the corresponding NO_3^- analogue (**5**) was obtained *via* activation of the triammine complex with an aqueous solution of $AgNO_3$.

The reaction between $[Pt(NH_3)_3(9\text{-MeA-}N7)]^{2+}$ and *trans*-$[Pt(H_2O)_2(NH_3)_2]^{2+}$ as perchlorates and nitrates was performed at a ratio of 2:1, yielding white precipitates. After recrystallization from water, crystals suitable for X-ray crystallography of the trinuclear perchlorate salt were successfully isolated. In the crystals of compound **7**, two $[Pt(NH_3)_3(9\text{-MeA-}N7)]$ units are bonded to the central Pt^{II} atom in a head–tail fashion.

$[Pt(NH_3)_3(9\text{-MeA-}N7)](NO_3)_2$ (5)

The structure of the cation of $[Pt(NH_3)_3(9\text{-MeA-}N7)](NO_3)_2$ (**5**) is shown in **Figure 1**. As in complex **4**, the platinum atom is square-planar coordinated by three NH_3 ligands and by the *N7*-coordinated 9-methyladenine ligand. All four Pt–N distances are essentially identical, while both N–Pt–N *trans* angles are slightly smaller (by *ca*. 0.5° and 2°) than in **4**.

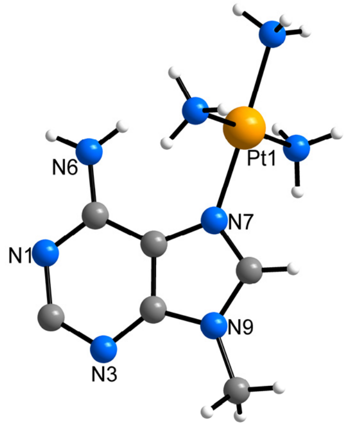


Figure 1. Structure of $[Pt(NH_3)_3(9\text{-MeA-}N7)]^{2+}$cation of 5

In crystals of **5**, the cations and the nitrate ions are connected by a network of N–H···O as well as N–H···N hydrogen bonds. In its crystal structure three types of interaction involving the perchlorate ions can be observed, realized with (a) NH_3 groups, (b), the exocyclic amino group *N6'*, and (c), the aromatic protons (at *C2* and *C8*). In contrast to the crystal packing of **4**, where perchlorate anions are present in the proximity of the *N1–N6* sites, the crystal packing of the nitrate salt shows interbase pairing (see **Figure 2**).

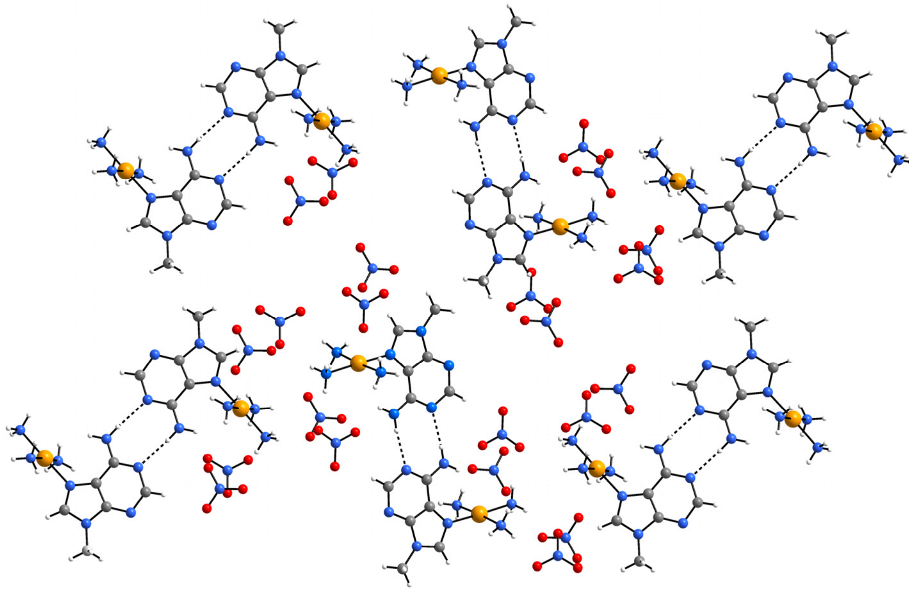
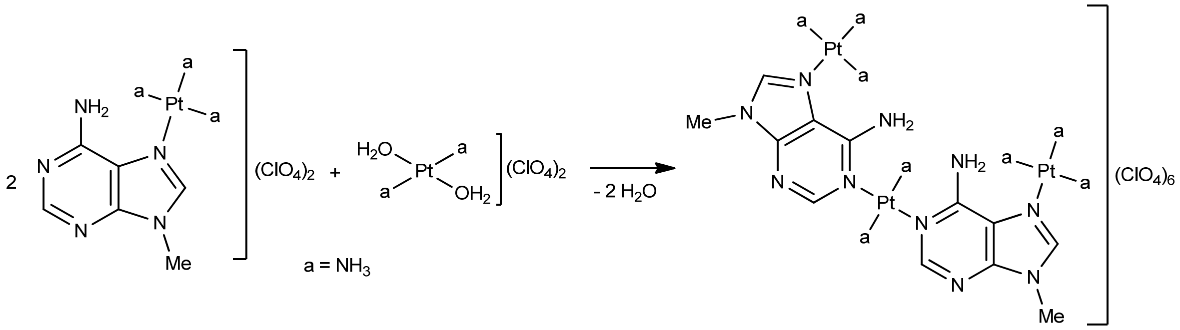


Figure 2. Crystal packing of $[(NH_3)_3Pt(9\text{-}MeA)](NO_3)_2$ (5)

trans-$[(NH_3)_2Pt\{(N1\text{-}9\text{-}MeA\text{-}N7)Pt(NH_3)_3\}_2](ClO_4)_6 \cdot 2H_2O$ (4)

The general synthetic route of the trinuclear complex **4** is presented in the **Scheme 2**.



5 **6'** **7**

Scheme 2

The obtained trinuclear complex **7** was characterized by spectroscopic methods (^1H, ^{13}C and ^{195}Pt NMR, IR), elemental analysis and ESI-MS mass spectrometry. Furthermore, the molecular structure was established by X-ray diffraction and also DFT calculations were performed as well.

***trans*-[$(NH_3)_2$Pt[(*N1*-9-MeA-*N7*)Pt$(NH_3)_3$]$_2$]$(ClO_4)_6\cdot 2H_2O$ (7)**

Molecular structure of **7**, presented in **Figure 3**, possesses an inversion center (Pt2 atom). The crystal packing of **7** is shown in **Figure 4**.

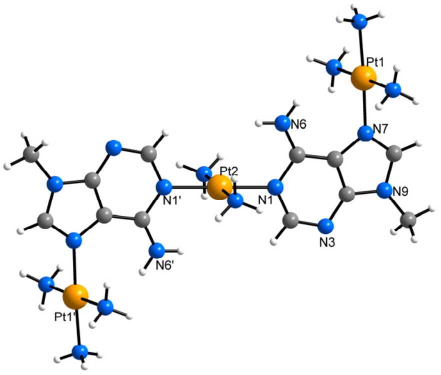


Figure 3. Molecular structure of 7

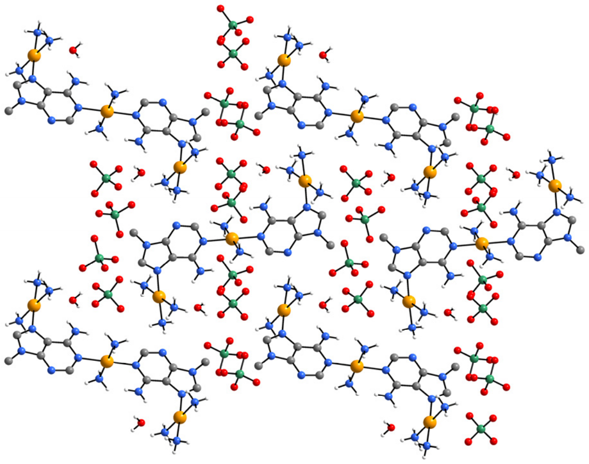
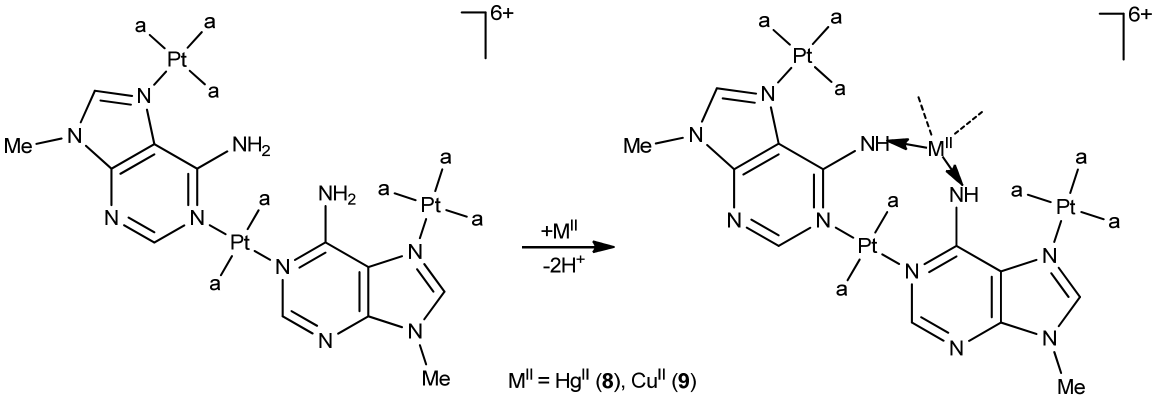


Figure 4. Crystal packing of 7

In the molecular structure of **4** the two 9-MeA entities bind to transplatin through the *N1* donor atoms, adopting a head-tail configuration. The Pt1–*N7* and Pt2–*N1* bond lengths are 1.99 Å and 2.01 Å, respectively. Furthermore, the angle between the two vectors Pt2–*N1* and Pt1–*N7* is 76°. The crystal packing is dominated by short contacts.

Heteronuclear complexes

By reacting the trinuclear complex **7** with two equivalents of $M^{II}(OCOMe)_2$ in aqueous solution (Hg^{II} and Cu^{II}) complexes *trans*-[$(NH_3)_2$Pt[(*N1*-9-MeA$^-$-*N6,N7*)Pt$(NH_3)_3$]$_2$ {Hg$(H_2O)_2$}]$(ClO_4)_6$ (**8**) and *trans*-[$(NH_3)_2$Pt[(*N1*-9-MeA$^-$-*N6,N7*)Pt$(NH_3)_3$]$_2$ {Cu$(H_2O)_2$}]$(ClO_4)_6$ **(9)** were obtained. The general reaction route is presented in **Scheme 3**.



Scheme 3

Heteronuclear complexes **8** and **9** were isolated, and their molecular structures were established by X-ray diffraction, while for the Hg^{II} complex (**8**) ^1H NMR spectrum was recorded as well.

Molecular structures of 8 and 9

From the reaction of the head-tail oriented Pt_3 parent molecule with M^{II}, the resulted heteronuclear complexes **8** and **9** (see below) adopt head-head orientation due to the formation of M–*N6* bond (**Figure 5**).

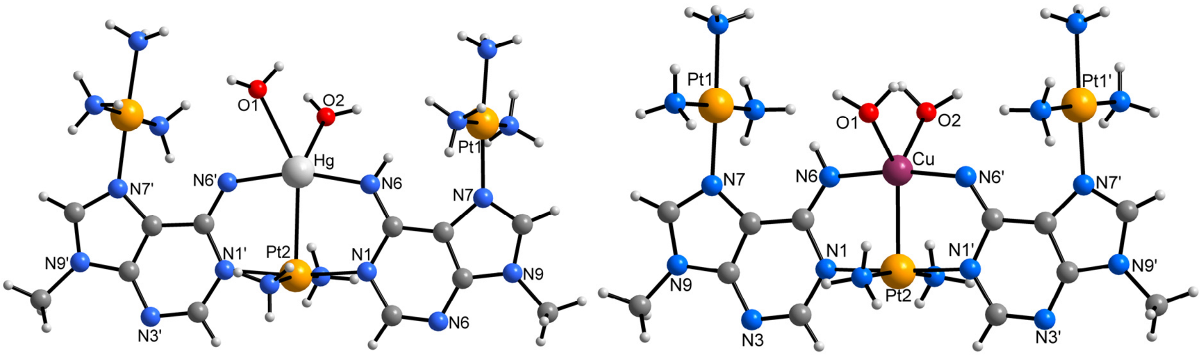


Figure 5. Molecular structures of 8 (left) and 9 (right)

In the molecular structures of complexes **8** and **9** the two 9-MeA moieties are connected *via* the Pt2 and Hg^{II}/Cu^{II} atoms, showing also intermetallic contacts; thus, each structure contain two five-membered cycles (CN_2PtM; M = Hg^{II} and Cu^{II}). The Pt–M interatomic distances are 2.80(7) Å (**8**) and 2.54(1) Å (**9**), respectively, while the Cu–*N6* bond lengths (1.92(8) Å) are shorter by *ca*. 0.12 Å than the corresponding Hg–*N6* (2.04 (1) Å), as expected. As compared to the parent Pt_3 cation (**7**), the Pt2–*N1* and Pt1–*N7* bond lengths and the Pt2–M–*N6* angle shows no significant differences.

Chapter III.
Original contributions on coordination chemistry of theophylline

Aim of the Topic

Interactions of metal ions with theophylline may serve as models for describing metal-DNA interactions, since theophylline can act as a model for guanine and guanosine.

The aim of this subject was to synthesize and characterize transition metal complexes of theophylline. Our ongoing research was focused on Cu^{II}, Zn^{II} and Cd^{II} complexes that consist of the corresponding metal ions, *N7*-coordinated theophylline and amines or aminoalcohols acting as co-ligands and deprotonating agents.

As auxiliary ligands, amines where chosen because the following reasons:

- A basic media is needed for deprotonate the theophylline, and we are able to use them as base, due their lone pair of electrons localized on N atoms. In the case of heterocyclic amines (bpy and phen), triethylamine was used for deprotonation of theophylline;
- They coordinate fairly readily to transition metal ions;
- They can stabilize the compounds formed, by making hydrogen bonds (*e.g.* intermolecular hydrogen bonds with the O atoms of theophylline moieties), and by forming a network of hydrogen bonds with the lattice water molecules, thus, favouring the formation of crystalline products, from which single-crystals suitable for X-ray diffraction can be obtained;
- Last but not least, most of them are water soluble, and can be introduced easily in the aqueous system, thus, avoiding the use of other (more expensive, toxic etc.) solvents.

Results and Discussion

The coordination compounds of theophylline were prepared in good yields *via* two different synthetic routes: by classical methods described in the literature, and through hydrothermal synthesis. In all synthesized compounds, theophylline coordinates through the *N7* donor site, confirmed by X-ray measurements for some compounds. The most relevant information obtained from IR spectra of theophylline complexes are given by the organic ligands bound to the metal centers, as compared to the free ligands. As described for each compound, both strong stretching vibration of *C6*(O) and *C2*(O) carbonyl groups show negative shifts, as result of coordination and the involvement of these groups to intra- or intermolecular hydrogen bonds [15, 16, 17]. Thus, it can be used for proving the coordination of theophylline to the metal.

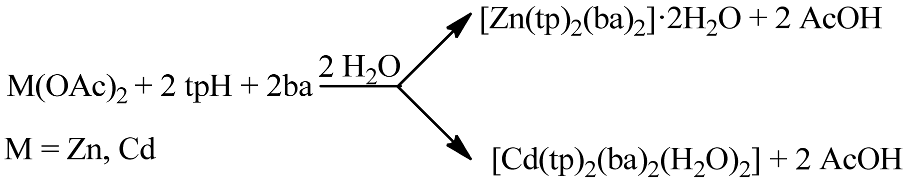
The thermogravimetric curves of synthesised compounds indicate a stepwise decomposition. First, the water molecules are released (where present), then the co-ligand are released (*e.g.* the relatively weakly bonded monoamines), followed by the pyrolysis of the organic material (*e.g.* the theophyllinato moieties) leading to a residuum of metal-oxides.

Two major observations can be noticed from the NMR measurements: first, the absence of the *N7*H resonance from the ^{1}H-NMR spectrum of the complexes in inorganic solvents (found at *ca.* 14 ppm in free theophylline), proving that theophylline coordinates in the deprotonated form; second, the resonances of protons of CH_3 groups undergo a chemical shift due to the changes of the electron density of purine system after coordination.

Coordination compounds with aliphatic monoamines

$[Zn(tp)_2(ba)_2]\cdot 2H_2O$ (10) and $[Cd(tp)_2(ba)_2(H_2O)_2]$ (11)

Both compounds were obtained as white precipitates by reacting a theophylline–benzylamine mixture with an aqueous solution of the corresponding metal(II) acetate. **Scheme 4** illustrates the reaction pathway:



$$M(OAc)_2 + 2\ tpH + 2ba \xrightarrow{2\ H_2O} \begin{cases} [Zn(tp)_2(ba)_2]\cdot 2H_2O + 2\ AcOH \\ [Cd(tp)_2(ba)_2(H_2O)_2] + 2\ AcOH \end{cases}$$

M = Zn, Cd

Scheme 4.

Although single-crystals could not been obtained, their most probable molecular structure are determined by elemental analysis, infrared spectra, thermoanalytical investigations and NMR spectra.

^{1}H NMR analysis of complex in $CDCl_3$ at 400 MHz indicates a 1:1 theophylline : benzylamine stoichiometry. The ^{1}H spectrum is presented in **Figure 6**.

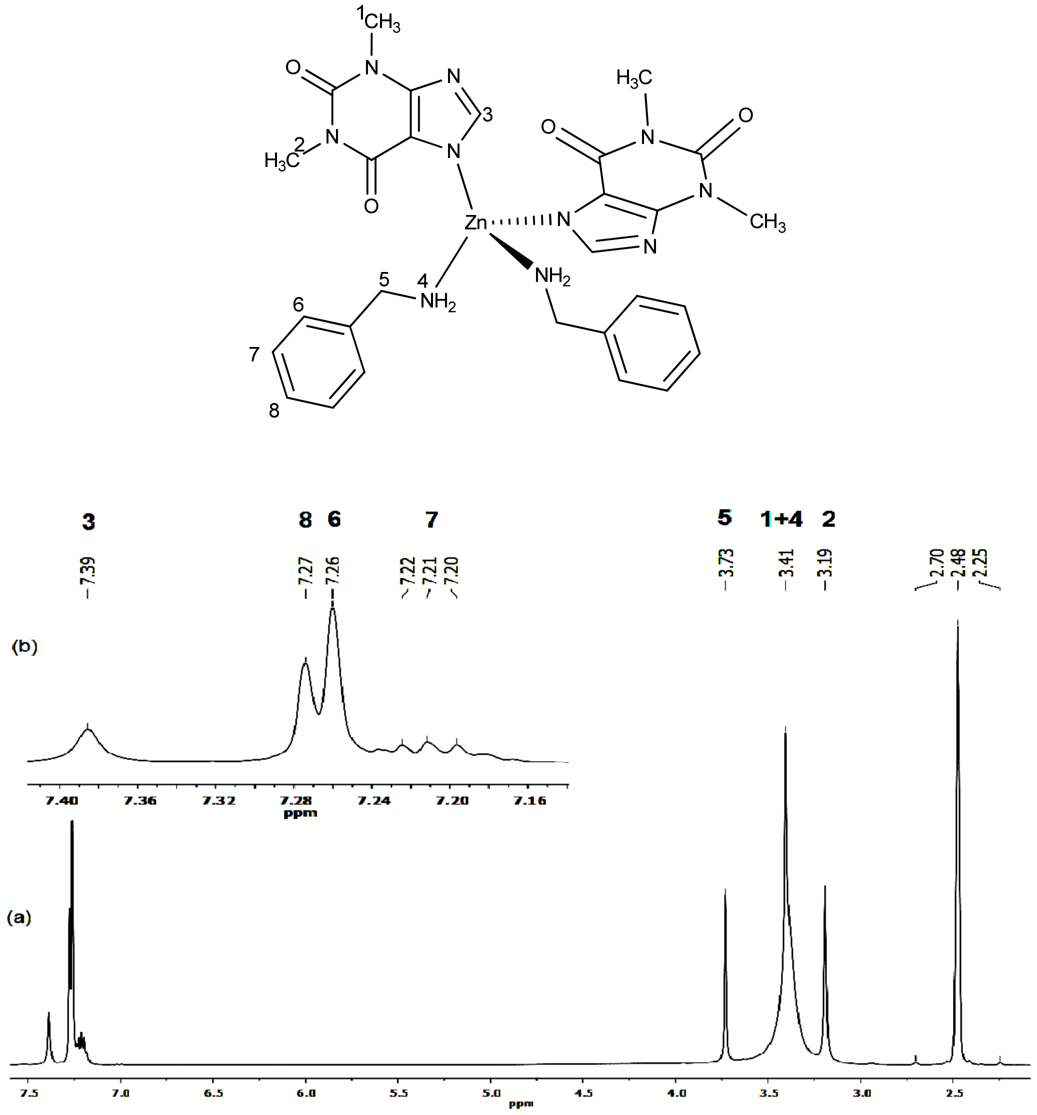


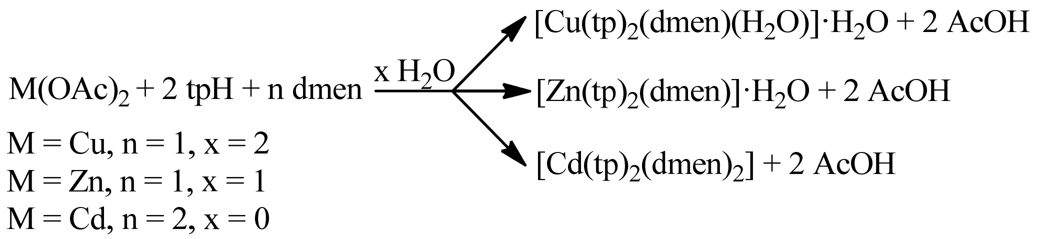
Figure 6. ^{1}H NMR spectrum of $[Zn(tp)_2(ba)_2]\cdot 2H_2O$ (10) (in $CDCl_3$, at 200 MHz)

Coordination compounds with aliphatic N,N-chelating diamines

Complexes of Zn^{II}, Cd^{II} and Cu^{II} with some ethylenediamine derivatives, namely N,N-dimethyl-ethylenediamine (dmen) and N,N,N’,N’-tetramethyl-ethylenediamine (tmeda) were synthesised and characterized.

$[Cu(tp)_2(dmen)(H_2O)]\cdot H_2O$ (13), $[Cd(tp)_2(dmen)_2]$ (14) and $[Zn(tp)_2(dmen)]\cdot H_2O$ (15)

The mixed-ligand theophylline complexes of Zn^{II}, Cd^{II} and Cu^{II} with N,N-chelating diamines were prepared by adding an aqueous solution containing the metal salt and amine to a theophylline–amine aqueous solution (M^{II} : th : amine = 1 : 2 : 2), according to **Scheme 4**.



Scheme 4

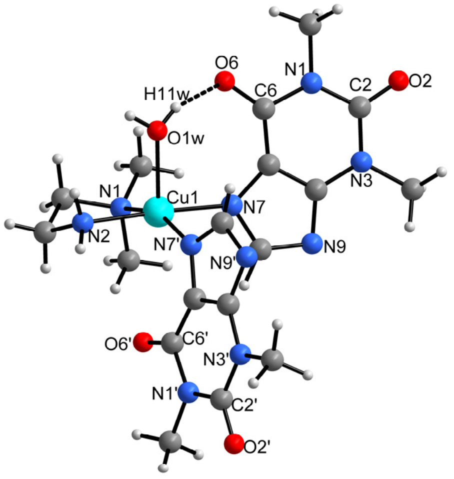


Figure 7. Molecular structure of [Cu(tp)$_2$(dmen)(H$_2$O)]·H$_2$O (13)

Bond lengths (Å)		Bond angles (°)	
Cu1–N7a	1.997(2)	**N1–Cu1–N7a**	92.4(8)
Cu1–N7b	1.994(2)	**N1–Cu1–N7b**	157.9(8)
Cu1–N1	2.080(2)	**N2–Cu1–N7a**	174.9(9)
Cu1–N2	2.008(2)	**N2–Cu1–N7b**	92.6(9)
Cu1–O1w	2.209(2)	**N7a–Cu1–N7b**	89.6(8)

The crystal packing of [Cd(tp)$_2$(dmen)$_2$] (**14**) is characterized by the lack of intermolecular hydrogen bonds, thus, the structure is governed by weak intermolecular C–H···O (d(H···O) = 2.27 Å d(C···O) = 3.25 Å, ∠(C–H···O) = 169.4°) and π–π stacking interactions. Stacking interaction between rings A and B is of *ca.* 3.6 Å, as shown in **Figure 8**.

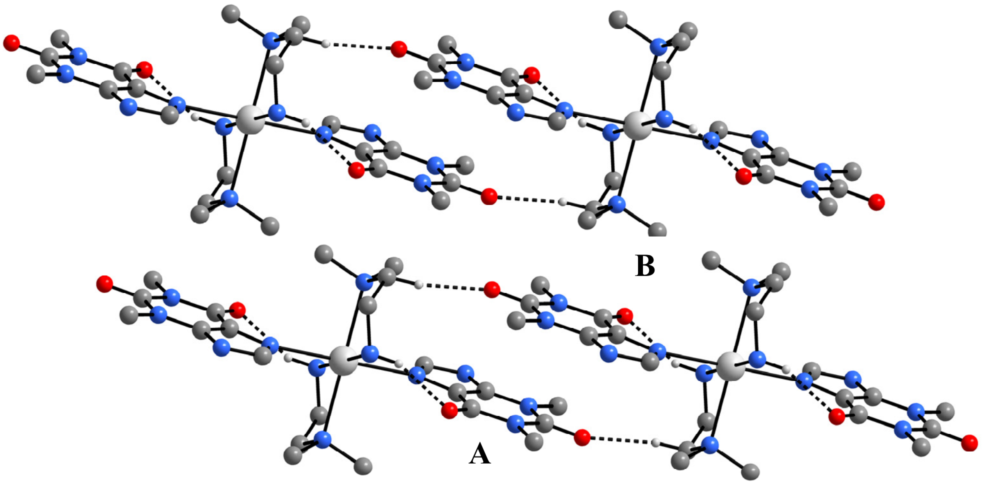


Figure 8. The crystal packing of [Cd(tp)$_2$(dmen)$_2$] (14)

$[Cu(tp)_2(tmeda)]\cdot 2H_2O$ (16) and $[Cu(tp)_2(tmeda)(H_2O)]\cdot 0.5H_2O$ (17)

As can be seen in **Figure 9**, the complexes are best described containing the Cu^{II} ion in a distorted square-pyramidal environment.

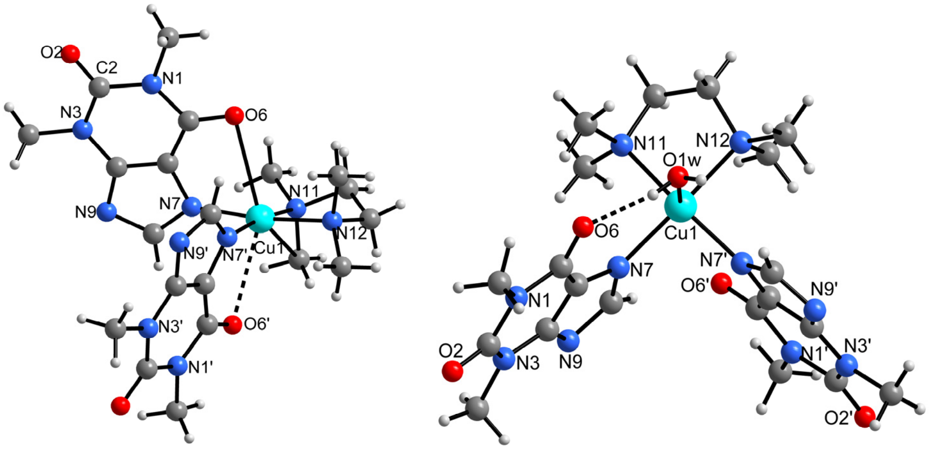


Figure 9. View of the coordination environment in compounds $[Cu(tp)_2(tmeda)]\cdot 2H_2O$ (16) (left) and $[Cu(tp)_2(tmeda)(H_2O)]\cdot 0.5H_2O$ (17) (right)

The Addison parameter (τ) [18], expressed as (β−α)/60, where β and α correspond to the highest two angles and the τ values of square-based-pyramidal and trigonal-bipyramidal extremes are 0 and 1, respectively, can be used to describe the coordination geometry of complex. In the case of complex **17**, the N7–Cu1–N12 and N7'–Cu1–N11 angles are 170.10(5)° and 169.2(4)°, respectively, leading to a τ value of 0.015. Thus, this value unequivocally confirms a square-pyramidal geometry of Cu^{II} in **17**.

Figure 10 shows the formation of one-dimensional zigzag chains in complex **16**, interconnected by O1w–H11w⋯N9' and O2w–H21w⋯N9 interactions, the pairs of chains lead to a three-dimensional supramolecular scaffold.

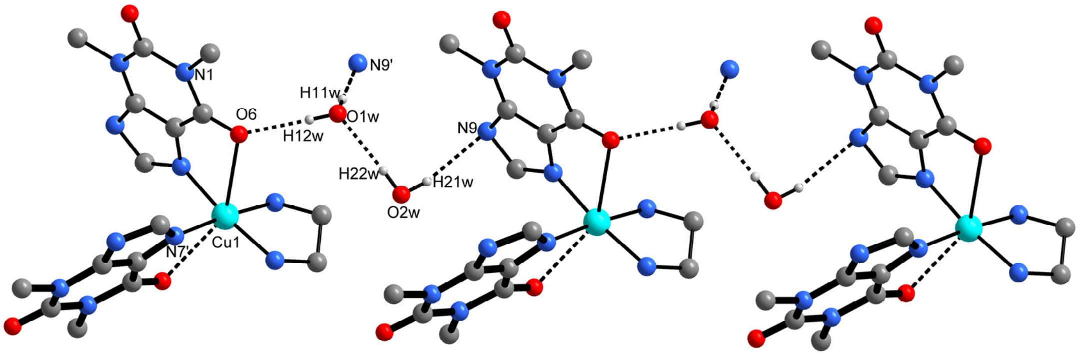


Figure 10. Extended hydrogen bond network formed with the involvement of the uncoordinated water molecules and theophylline moieties in compound 16.

In compound **17** two [Cu(tp)$_2$(tmeda)(H$_2$O)] units are connected *via* their oxygen atoms of C2’–O2’ carbonyl groups of two theophylline moieties through the O1w water molecule, which acts as a bridge (see **Figure 11**). Thus, dimeric {tmeda(Cu)(tp)$_2$···H$_2$O···Cu(tp)$_2$(tmeda)} units are formed.

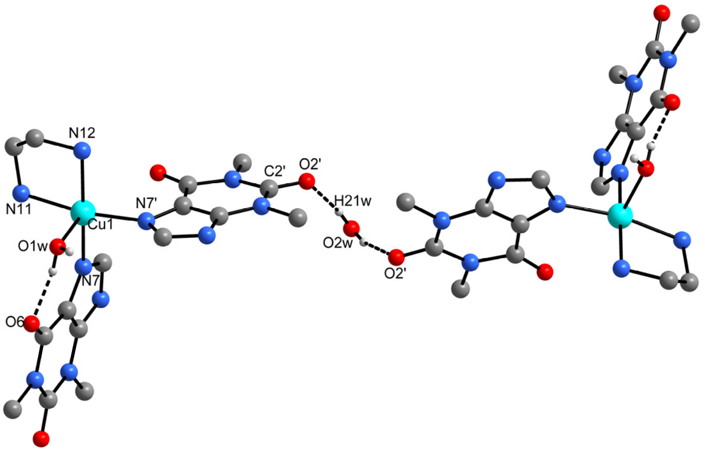


Figure 11. Dimeric unit formed *via* hydrogen bonds in compound 17

Crystal packing of [Cu(tp)$_2$(dphen)(H$_2$O)]·5H$_2$O (**18**) consists of an extended network of hydrogen bonds, as illustrated in **Figure 12**.

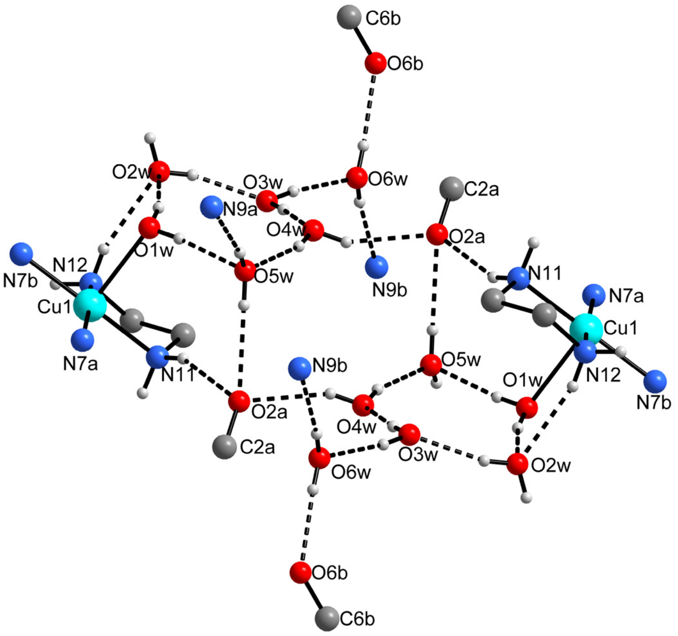


Figure 12. **Extended hydrogen bonding interactions between two Cu(dphen) units in 18, realized through {H$_2$O}$_5$ rings and oxygen atoms of C2a(O2a) carbonyl groups**

Excepting the relatively moderate N11–H11a···O2a bond, with an N···O interatomic distance of *ca*. 3.15 Å and an angle of 156.6°, all other hydrogen bonds involving the water molecules surrounding the complex are relatively strong, with distances of 2.66–2.99 Å between heteroatoms and angles of 160–177°. Weak and strong hydrogen bonding interactions determine a highly dimensional supramolecular structure. In addition, stacking interactions between theophylline moieties of adjacent molecules are present, with d_{A-B} of *ca.* 3.4 Å.

Coordination compounds with aliphatic triamines

Reactions of aqueous solutions of Zn^{II} and Cd^{II} acetates with aqueous theophylline–dien mixtures (molar ratio tp:dien = 2:1) lead to isostructural $[M(tp)_2(dien)]\cdot 2H_2O$ complexes, with the coordination geometry around the metal ions is between square-pyramidal and trigonal-bipyramidal extremes.

$$\mathrm{M(OAc)_2 + 2\ tpH + dien \xrightarrow{2\ H_2O} [M(tp)_2(dien)]\cdot 2H_2O + 2AcOH}$$

M = Zn or Cd

The coordination geometry of the five-coordinated Zn^{II} and Cd^{II} ions in compounds $[Zn(tp)_2(dien)]\cdot 2H_2O$ (**20**) and $[Cd(tp)_2(dien)]\cdot 2H_2O$ (**21**), based on the Addison parameter (τ), can be described as an intermediate between square pyramidal and trigonal bipyramidal (τ = 0.483 for **20** and 0.487 for **21**), implying approximately 50% contributions of the two extremes. **Figure 13** illustrates the formation of supramolecular associations in **20** involving the O21w and O22w water molecules.

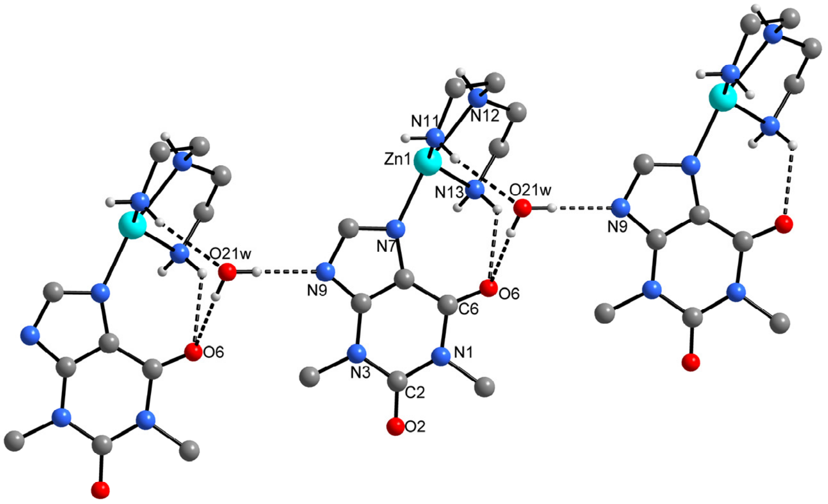


Figure 13. Supramolecular chains involving the O21w water of crystallization in 20

Coordination compounds with heterocyclic amines

Synthesis and characterization of mixed-ligand theophylline complexes, containing 2,2'-bipyridine (bpy) or o-phenanthroline (phen) was undertaken. The solid-state structure of $[Zn(tp)_2(bpy)]$ (**22**) shows that the Zn^{II} ions are coordinated by two anionic theophylline units and one chelating 2,2'-bipyridine ligand, displaying a tetrahedral ZnN_4 tetrahedral geometry. The bpy ligand is not exactly planar, showing a notable torsional angle (twist angle) between the two six-membered pyridine rings, of 8.2°. Bite angle of bpy ligand ($\angle_{N10–Zn–N10'}$) is in agreement with values found for similar Zn-bpy complexes. The crystal packing is dominated by weak or moderate interactions of type C–O···H, C–H···O and C–H···N formed between adjacent mononuclear units. Stacking interactions can be observed in the crystal packing: the neighboring $[Zn(tp)_2(bpy)]$ molecules are oriented as such that their theophylline moieties are oriented parallel to each other, along the *c* axis (see **Figure 14**), with an interplanar distance of 3.48 Å. Thus, intermolecular π–π stacking interactions assemble the complex molecules into supramolecular layers.

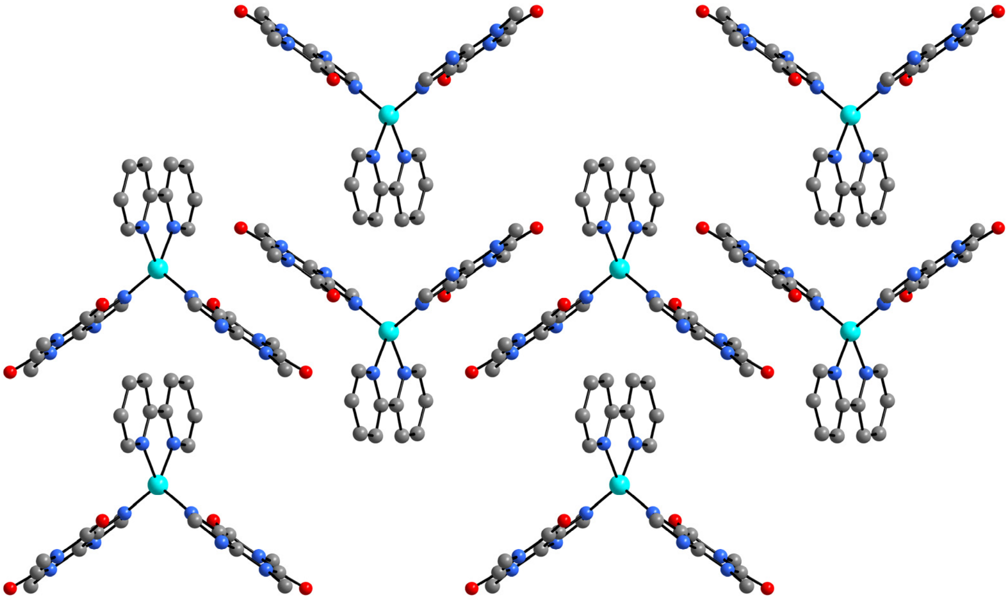


Figure 14. Crystal packing of 22 viewed along *a* axis

$[Cd_2(\mu\text{-ox})(OH)_2(tp)_2(bpy)_2]\cdot 2H_2O$ (23) and $[Cd_2(\mu\text{-ox})(OH)_2(tp)_2(phen)_2]$ (24)

Compounds $[Cd_2(\mu\text{-ox})(OH)_2(tp)_2(bpy)_2]\cdot 2H_2O$ (**23**) and $[Cd_2(\mu\text{-ox})(OH)_2(tp)_2 (phen)_2]$ (**24**) were obtained under hydrothermal conditions, with an interesting *in situ* formation of oxalate from acetate. In some cases, conversion of different ligands into oxalate (*e.g.* acetate [19] or pyrazine-2,3,5-tricarboxylic acid [20]) under hydrothermal conditions was observed. The two [Cd(tp)(bpy)(H_2O)] and [Cd(tp)(phen)(H_2O)] units bridged by a bisbidentate oxalate ion are oriented in an anti position.

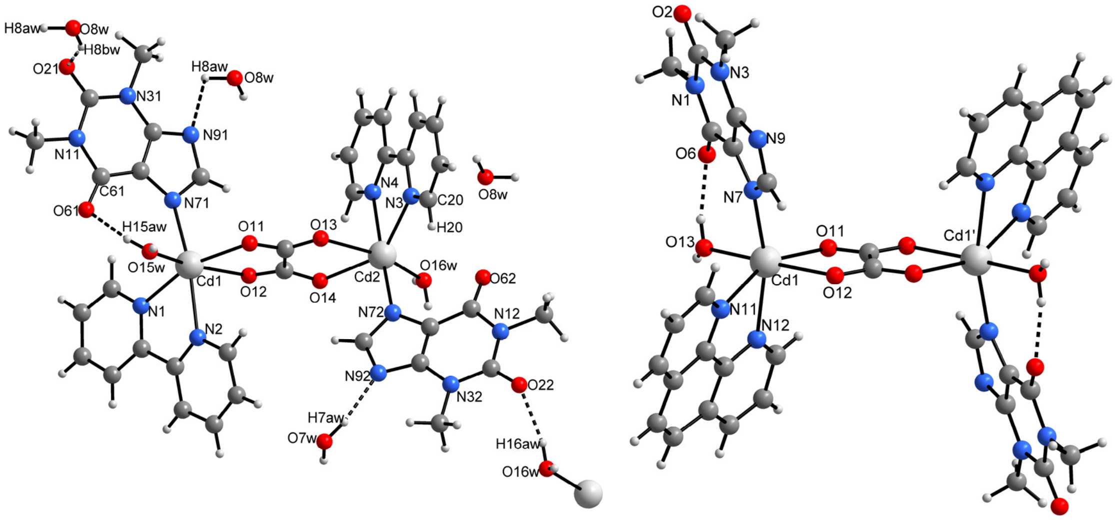


Figure 15. View of structure of 23 (left) and 24 (right)

Packing of **23** is stabilized by a tridimensional hydrogen bond network, achieved by the envolvement of *N9* donor sites of theophylline, coordinated water molecules, lattice water molecules.

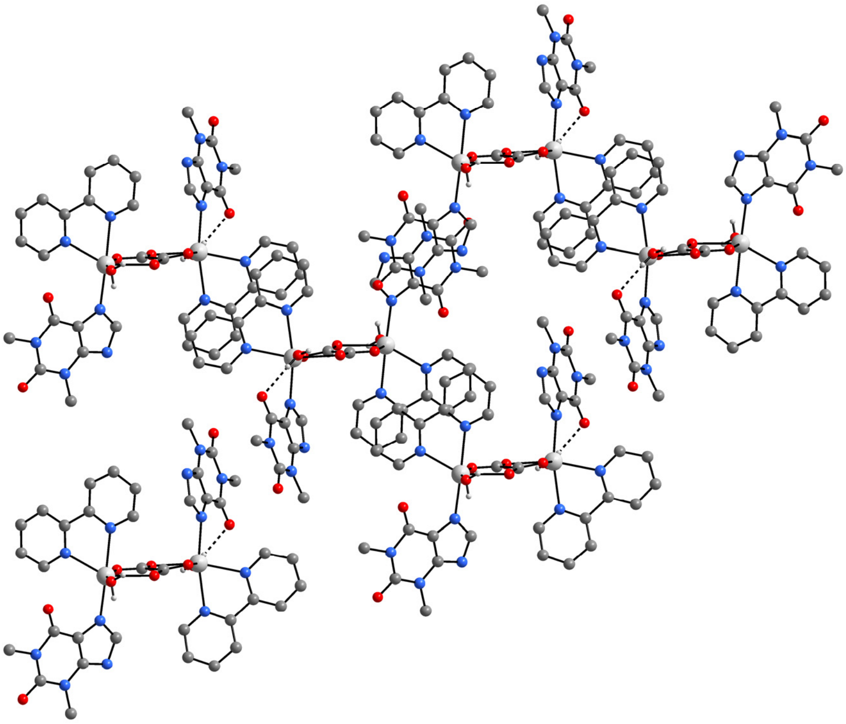


Figure 16. Crystal packing of 23, viewed along *a* axis

Similarly with the [Zn(tp)$_2$(bpy)] (**22**) complex, in which the bpy ligands are not planar, in [Cd$_2$(μ-ox)(OH)$_2$(tp)$_2$(phen)$_2$] (**24**) the dihedral angle between the least-square planes defined by the two C$_5$N rings of phen ligands is about 6.4°. Its crystal packing is mainly stabilized by a tridimensional hydrogen bonding network. **Figure 17** illustrates a part of this network, showing a bidimensional supramolecular motif viewed along *b* axis, realized through the coordinated water molecules acting as bridges between *N9* and *O6* acceptor sites of theophylline ligands of adjacent molecules.

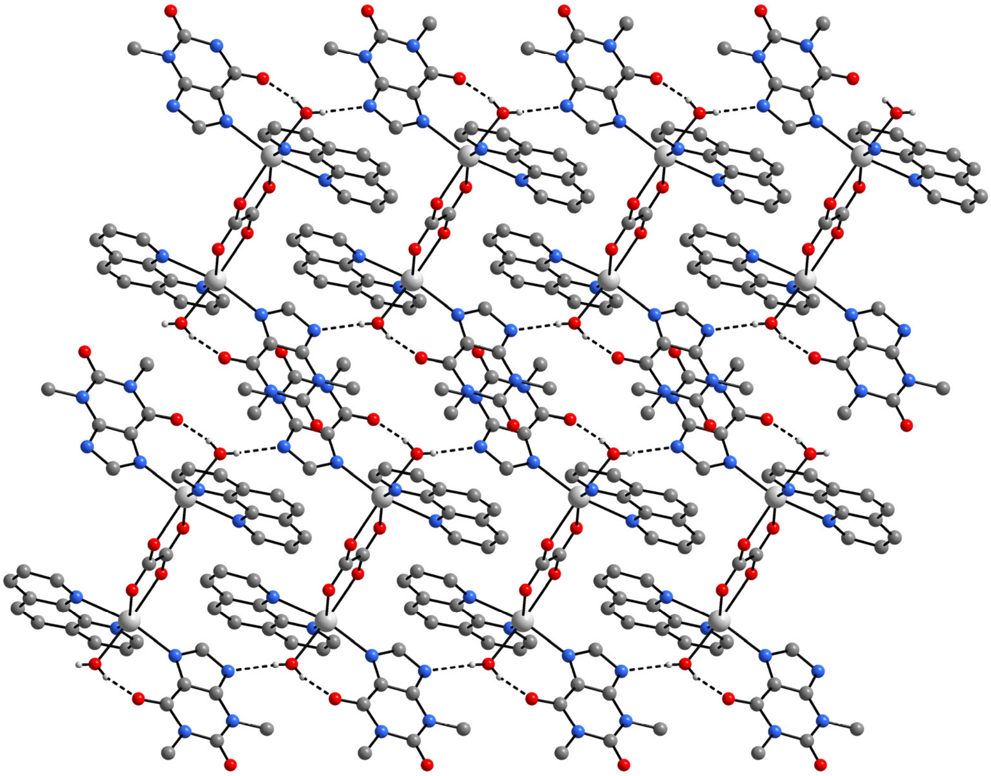


Figure 17. Twodimensional hydrogen bond network packing of 24, viewed along *b* axis

Conclusions

This study presents the synthesis, characterization of new mixed-ligand coordination compounds of Cu^{II}, Zn^{II}, and Cd^{II} with theophylline and aliphatic and heterocyclic amines and aminoalkohols. For some compounds, theoretical study using DFT methods has been carried out using their solid-state structures as starting points for optimizations.

The theophylline ligands are deprotonated at the *N7* most acidic site, by the basic co-ligands, leading to *N7*–coordinated theophyllinato complexes. The crystal packing of structurally characterized compounds reveal that the structures are stabilized by the presence of O—H···O, O—H···N and/or N—H···O hydrogen bonds involving the theophylline and amine ligands and uncoordinated water molecules (where present). Frequently, stacking interactions occur between adjacent theophylline ligands of neighboring molecules.

In the case of one pot hydrothermal synthesis of mixed-ligand complexes containing heterocyclic amines as co-ligands, two novel dinuclear theophylline complexes of Cd^{II} containing oxalate bridge formed in situ under hydrothermal conditions were obtained and structurally characterized.

Attempts on obtaining ternary Cd–theophylline–benzylamine systems, even under hydrothermal conditions (with stoichiometric Cd^{II}:tp:ba ratio) failed; instead, $[Cd(tp)_2(H_2O)_4]$ compound was formed. As a perspective, by changing the reaction conditions, like increasing the amount of benzylamine, formation of mixed-ligand ba-tp complexes (like of type $[Cd(tp)_2(ba)_2(H_2O)_2]$) might be feasible.

Theoretical investigations at B3LYP/LANL2DZ or CRENBL level of the theory were proved to be efficient in optimizing structural geometries of these systems.

Some results on compounds presented in the present thesis were published in the last years; however, there are many experimental results (as in the case of several, structurally and spectroscopically characterized compounds) which are still not published.

List of synthesised compounds

1	**9-MeA**
2	**$[\mathrm{PtCl_3(9\text{-}MeAH\text{-}}\mathit{N7}\mathrm{)}]$**
3	**$[\mathrm{Pt(NH_3)_3(9\text{-}MeA\text{-}}\mathit{N7}\mathrm{)]Cl_2}$**
4	**$[\mathrm{Pt(NH_3)_3(9\text{-}MeA\text{-}}\mathit{N7}\mathrm{)](ClO_4)_2}$**
5	**$[\mathrm{Pt(NH_3)_3(9\text{-}MeA)](NO_3)_2}$**
6	***trans*-$[\mathrm{Pt(NH_3)_2Cl_2}]$**
7	***trans*-$[\mathrm{(NH_3)_2Pt[(}\mathit{N1}\text{-}\mathrm{9\text{-}MeA\text{-}}\mathit{N7}\mathrm{)Pt(NH_3)_3]_2](ClO_4)_6\cdot 2H_2O}$**
8	***trans*-$[\mathrm{(NH_3)_2Pt[(}\mathit{N1}\text{-}\mathrm{9\text{-}MeA^{-}\text{-}}\mathit{N6,N7}\mathrm{)Pt(NH_3)_3]_2\{Hg(H_2O)_2\}](ClO_4)_6}$**
9	***trans*-$[\mathrm{(NH_3)_2Pt[(}\mathit{N1}\text{-}\mathrm{9\text{-}MeA^{-}\text{-}}\mathit{N6,N7}\mathrm{)Pt(NH_3)_3]_2\{Cu(H_2O)_2\}](ClO_4)_6}$**
10	**$[\mathrm{Zn(tp)_2(ba)_2]\cdot 2H_2O}$**
11	**$[\mathrm{Cd(tp)_2(ba)_2(H_2O)_2}]$**
12	**$[\mathrm{Cd(tp)_2(H_2O)_4}]$**
13	**$[\mathrm{Cu(tp)_2(dmen)(H_2O)]\cdot H_2O}$**
14	**$[\mathrm{Cd(tp)_2(dmen)_2}]$**
15	**$[\mathrm{Zn(tp)_2(dmen)]\cdot H_2O}$**
16	**$[\mathrm{Cu(tp)_2(tmeda)]\cdot 2H_2O}$**
17	**$[\mathrm{Cu(tp)_2(tmeda)(H_2O)]\cdot 0.5H_2O}$**
18	**$[\mathrm{Cu(tp)_2(dphen)(H_2O)]\cdot 5H_2O}$**
19	**$[\mathrm{Zn(tp)_2(dphen)]\cdot 1.5H_2O}$**
20	**$[\mathrm{Zn(tp)_2(dien)]\cdot 2H_2O}$**
21	**$[\mathrm{Cd(tp)_2(dien)]\cdot 2H_2O}$**
22	**$[\mathrm{Zn(tp)_2(bpy)}]$**
23	**$[\mathrm{Cd_2(\mu\text{-}ox)(OH)_2(tp)_2(bpy)_2]\cdot 2H_2O}$**
24	**$[\mathrm{Cd_2(\mu\text{-}ox)(OH)_2(tp)_2(phen)_2}]$**
25	**$[\mathrm{Zn(tp)_2(ea)_2]\cdot H_2O}$**
26	**$[\mathrm{Zn(tp)_2(pa)_2]\cdot H_2O}$**

List of publications

1. B. Mihály, E. Forizs, I. Silaghi-Dumitrescu, *Studia Univ. Babes-Bolyai, Chemia*, **2007**, *LII*(4), 111−116.

2. B. Mihály, E. Forizs, A.-Z. Kun, I. Silaghi-Dumitrescu, *Acta Cryst.,* **2009**, *E65*, m579.

3. B. Mihály, E. Forizs, I. Silaghi-Dumitrescu, *Proceedings of the 9th International Symposium on Metal Elements in Environment, Medicine and Biology (M.E.E.M.B.)*, Tome IX, 126−129, Cluj-Napoca, October 16−17, **2009**.

4. B. Mihály, A.-Z. Kun, E. Forizs, A. Patrut, I. Silaghi-Dumitrescu, *Studia Univ. Babes-Bolyai, Chemia*, **2010**, *XLV*(2), 125−131.

5. Cs. Nagy, C. Someșan, A.-Z. Kun, B. Mihály, E. Forizs, L. David, *Studia Univ. Babes-Bolyai, Chemia*, **2010**, *XLV*(2), 265–272.

6. Cs. Fábri, E. Mátyus, T. Furtenbacher, L. Nemes, B. Mihály, T. Zoltáni, A. G. Császár, *J. Chem. Phys.*, **2011**, *135*, 094307-1–094307-19.

7. T. Mihály, M. Bette, B. Mihály, J. Schmidt, H. Schmidt, D. Steinborn, *J. Organomet. Chem.*, **2013**, *739*, 57–62.

Bibliography (Abstract)

---

1. J. A. R. Navarro, B. Lippert, *Coord. Chem. Rev.*, **1999**, *185–186* , 653.
2. M. S. Lüth, M. Willermann, B. Lippert, *Chem. Commun.*, **2001**, 2058.
3. B. Lippert, H. Schöllhorn, U. Thewalt, *Inorg. Chim. Acta*, **1992**, *198–200*, 723.
4. D. J. Hodgson, *Prog. Inorg. Chem.*, **1977**, *23*, 211.
5. L. G. Marzilli, T. J. Kistenmacher, *Acc. Chem. Res.*, **1977**, *10*, 46.
6. N. S. Begum, H. Manohar, *Polyhedron*, **1994**, *13*, 307.
7. W. J. Birdsall, M. S. Zitzman, *J. Inorg. Nucl. Chem.*, **1979**, *41*, 116.
8. W. J. Birdsall, *Inorg. Chim. Acta*, **1985**, *99*, 59.
9. P. Umapathy, R.A. Shaikh, *J. Indian Chem. Soc.*, **1985**, *62*, 103.
10. J. Madarász, P. Bombicz, M. Czugler, G. Pokol, *Polyhedron*, **2000**, *19,* 457.
11. D. Lichtenberg, F. Bergmann, Z. Neiman, *J. Chem. Soc. (C)*, **1971**, 1676.
12. E. G. Talman, W. Brunig, J. Reedijk, A. L. Spek, N. Veldman, *Inorg. Chem.*, **1997**, *36*, 854.
13. N. Hadjiliadis, T. Theophanides, *Inorg. Chim. Acta*, **1976**, *16,* 67.
14. G. B. Kauffman, D. O. Cowan, *Inorg. Synth.,* **1963**, *7*, 239.
15. P. Bombicz, J. Madarász, E. Forizs, M. Czugler, G. Pokol, S. Gál, A. Kálmán, *Z. Kristallogr.*, **2000**, *215*, 317.
16. E. Forizs, L. David, O. Cozar, V. Chis, G. Damian, J. Csibi, *J. Mol. Struct.*, **1999**, *482–483*, 143.
17. M. B. Cingi, A. M. M. Lanfredi, A. Tiripicchio, M. T. Camellini, *Transition Met. Chem.*, **1979**, *4*, 221.
18. A. W. Addison, T. N. Rao, J. Reedijk, J. van Rijn, G. C. Verschoor, *J. Chem. Soc. Dalton Trans.*, **1984**, 1349.
19. W.-J. Di, S.-M. Lan, Q. Zhang, Y.-X. Liang, *Acta Cryst.*, **2011**, *E67*, m1436.
20. F.-Q. Wang, W.-H. Mu, X.-J. Zheng, L.-C. Li, D.-C. Fang, L.-P. Jin, *Inorg. Chem.*, **2008**, *47*, 5225.